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ALTERATIONS IN TISSUE METABOLISM (THE LUNG) WITH INJURY AND SHOCK

Annual Summary Report

ARTHUR E. BAUE, M.D.

July 15, 1973

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Washington University School of Medicine

and

The Jewish Hospital of St. Louis
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Alterations in cell function during shock with decreased mitochondrial metabolic capability, increased ATPase activity and increased mitochondrial Na and decreased K have all been corrected by treatment. These changes and decreased ATP levels in cells have suggested possible impairment of the ability of cell membranes to carry out active transport and maintain cell volume. The present studies were carried out to measure cell membrane transport during and after shock.

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In the past year we have made considerable progress in providing basic information relevant to the objectives of this contract. Papers from our laboratory describing work supported by this contract have been presented at the American Association for the Surgery of Trauma, to the Fundamental Forum of the American College of Surgeons, the meeting of the Society of University Surgeons and the American Physiological Society at the Federation meeting in both the Fall and the Spring. Later in April we will be presenting a paper, "Alterations in Cell Membrane Transport during and after Shock" to the American Surgical Association. We also participated in a recent trauma workshop organized by the National Institute of General Medical Sciences in which we were asked to summarize the needs for future studies relevant to shock and circulation.

Much of what has been done during the previous contract period has been described in progress reports which will be summarized here.

a. The work on shock and the lung has culminated in our providing evidence that, at least in a canine model, hemorrhagic shock per se does not produce pulmonary lesions nor does it overtly damage the lung morphologically or functionally. This is in direct contrast to many previous reports from other laboratories indicating an entity which can be called "shock lung." This work was presented by Dr. Jerry Meyers to the American Association for the Surgery of Trauma in a paper entitled, "Does Hemorrhagic Shock Damage the Lung?" which will soon be published in the Journal of Trauma. In this manuscript we discuss the very real possibility that although hemorrhagic shock per se does not damage the lung, that it may decrease the metabolic ventilatory and circulatory reserve of the lung, and therefore may make it more susceptible to further insults or noxious factors. Thus shock could set the stage and then with sepsis, [illegible] overload, fluid retention, transfusion of old bank blood and many other factors, the picture of post-traumatic pulmonary insufficiency could be produced. We are now pursuing this in the laboratory by combining the shock insult with various other maneuvers following it to look into this possibility. We feel that this is extremely important because it may well be that many aspects of aggressive resuscitation in the treatment of shock and circulatory failure may actually in some situations intensify or produce the pulmonary lesions which are seen in the injured.

In altering the protocols we still find that we are unable to produce pulmonary lesions in dogs with hemorrhagic shock even though bank blood is used and other aspects which are considered to be deleterious have been tried. This should be continued because we would hope to be able to further substantiate

that hemorrhagic shock does not initially prove seriously deleterious to the lungs of individuals. There are probably, however, some subtle changes that do take place which may make the individual's lungs more sensitive to further injury such as with overventilation, overhydration and the like. Hopefully by putting this into perspective we can come to grips better with the prevention of post-traumatic pulmonary insufficiency rather than just dealing with it when it occurs. By careful dissection of the factors involved in post-traumatic pulmonary insufficiency, I feel that in the future we will probably alter our approach to the injured individual in order to prevent this occurrence rather than simply recognizing and dealing with it when it occurs.

b. The previously cited studies of energy levels present in cells during hemorrhagic shock were completed, at least in one phase, and Dr. Irshad Chaudry from our laboratory presented a paper at the Surgical Forum of the American College of Surgeons entitled, "Alterations in Adenosine Nucleotides in Hemorrhagic Shock." This study shows a progressive and considerable decline in high energy phosphate levels in various cell populations during hemorrhagic shock. At the present time we are now looking into reversibility of these changes with various treatment protocols.

We have now looked into the possibility of utilizing high energy phosphates as ATP in the treatment of shock and are developing some fascinating data which indicate that ATP can increase survival following hemorrhagic shock even when given during and after the insult. One of the problems in several previous studies by others which have been carried out in this area is that ATP when given is rapidly chelated. Therefore, it should not be usable as energy. However, we are giving ATP with magnesium so that it is already chelated and therefore could be available for energy utilization. There are many questions about this area of activity which remain to be answered; however, we are pursuing it vigorously and this may also be an exciting approach toward treatment.

We have now documented not only that energy levels are decreased, but also that survival can definitely be improved by giving ATP chelated with magnesium chloride. We have also now demonstrated that when ATP-magnesium chloride combination is given that the energy levels present within cells are increased. This work entitled, "ATP Depletion and Replenishment in Hemorrhagic Shock" has been submitted to the Surgical Forum of the American College of Surgeons for October, 1973.

We are going to pursue further the possibility of treating late circulatory failure with high energy phosphate bonds such as ATP in various forms and it may well be that we will soon be ready to launch a clinical study of this approach.

c. We have continued the work on the study of alterations in active transport of cations, particularly sodium and potassium in hemorrhagic shock. We have provided initial evidence that there is significant decrease in transport, particularly of the cell population being able to remove sodium and maintain potassium. Much of this work has now been completed and Dr. Sayeed and I presented a manuscript to the American Journal of Physiology entitled, "Na-K Transport in Rat Liver Slices in Hemorrhagic Shock." We are presently determining the reversibility of this depression of cell membrane transport. This change in transport could have a tremendous influence on the intact individual in that sodium may be moving into cells along with water following shock and injury and may, indeed, alter extracellular fluid volumes as originally proposed by Shires.

This work on cell membrane transport during shock has been continued and an abstract recently submitted which summarizes this work has been accepted by the American Surgical Association for presentation at their meeting in Los Angeles in April of this year. A summary of this work follows.

Alterations in cell function during shock with decreased mitochondrial metabolic capability, increased ATPase activity and increased mitochondrial Na and decreased K have all been corrected by treatment. These changes and decreased ATP levels in cells have suggested possible impairment of the ability of cell membranes to carry out active transport and maintain cell volume. The present studies were carried out to measure cell membrane transport during and after shock.

Awake albino rats bled to a mean blood pressure of 40 mm Hg until 25% of the shed blood had to be returned (predicted survival 50% if treated then) were sacrificed or treated with the remaining blood and an equal volume of Ringer's lactate and sacrificed an hour later. Livers were removed and 0.5 mm tissue slices prepared. Na and K were determined by atomic absorption spectroscopy, water by drying and extracellular space by inulin. Transport capability was measured in two ways. First, slices were cooled. This stops active transport and Na enters and K leaves cells. With rewarming, transport in normal tissue should begin again with Na pumped out and K into cells. Upon rewarming, Na contents decreased in eight unbled control animals from

c. (continued)

753.±23. mEq/kg dry tissue (Mean ± SEM) to 606.±28. and K increased from 95.±3. to 212.±9. Such cation movements did not occur in slices from 12 shock animals before or after treatment. Secondly, to avoid cold incubation, other slices were maintained at 37°C. Initially, Na increased and K decreased in all but with continued incubation in controls, Na then decreased from 538.±40. to 466.±16. and K increased from 119.±7. to 200.±8.,indicating active transport but in nine treated shock animals there was neither a decrease in Na (680.±24. to 733.±33.) nor an increase in K (92.±5. to 109.±6.). Intracellular water and Na were increased with shock.

Thus, with this form of shock, active cell membrane transport of Na and K was severely impaired, and water and Na entered cells. These changes were not rapidly corrected by treatment as were other altered cell functions and thus may be a limiting factor in severe shock.

This work compares beautifully with that carried out by Dr. Shires in which cell membrane potential has been measured and calculations made from it. We are now studying further the restoration to normal of these alterations with treatment.

d. We have begun to look into the matter of glucose transport across cell membranes during hemorrhagic shock. The initial findings are that there is no change in glucose transport, which is interesting in itself because a theory of biochemists and physiologists has been that as energy levels are decreased,such as the decreased ATP which we have determined, then glucose transport should be enhanced. We have found recently that insulin cannot augment this transport of glucose across cell membranes during prolonged hemorrhagic shock. This is a very exciting finding which we will have to further document and pinpoint.

Further work on glucose transport across cell membranes during hemorrhagic shock was then carried out substantiating that tissues from animals in shock seem to be relatively unresponsive to insulin and the reasons for this change are now being looked into. This now provides a very reasonable explanation for the tendency toward hyperglycemia and diabetic type picture which is seen in injured patients. We are now developing a preparation for septic shock and will begin by evaluating a preparation of the rat with cecal ligation to produce peritonitis and would like to look into the matter of glucose and insulin metabolism in such a preparation with sepsis. Several of these observations and studies are now being presented and submitted for publication, but we do not have definite information as yet as to where and when they will be published.

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In addition to the publications which will be listed which have resulted from work supported by this contract, we have also had the opportunity to present this work at a number of symposia and post-graduate courses around the country which, hopefully, will make this information available to others and to increase interest in and improve the care of the injured. The principal investigator gave a series of lectures at the Dallas Southern Clinical Society recently on studies of circulatory failure. He will give a lecture at a post-graduate course at the University of Kansas Medical Center in a few days on recent studies in circulatory failure. He will be chairman of a post-graduate course in Shock at the Spring Meeting of Surgeons in New York City. Later in the Spring there will be a lecture series at a meeting of the New York Chapter of the American College of Surgeons by the principal investigator on circulatory failure and several lectures will be given at the State University of New York in Syracuse on studies in circulatory failure. An additional lecture will be given at a post-graduate course at the University of Cincinnati School of Medicine in May on recent developments in the study and treatment of circulatory failure. These presentations will be derived in good part from data obtained under the studies supported by this contract in 1972.

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